1			
.2			Claims
3			
4		What v	we claim is:
5	_ 1		
Dro 6	u_	-1.	An endosomal lysing agent comprising a compound having one or more hydrolyzable
7		function	onal moieties and wherein said compound is capable of effecting the lysis of an endosome
8		in resp	onse to a change in pH.
9			•
10		2.	The endosornal lysing agent of claim 1, comprising a biocompatible compound.
11			
12 6 18	(131)	3.	The endosomal lysing agent of claim 1, comprising a biodegradable compound.
1 3			
13 14 15		4.	The endosomal lysing agent of claim 1, comprising a biocompatible and biodegradable
15		compo	ound.
S 16			
117	2	5.	An endosomal lysing agent comprising a compound having one or more hydrolyzable
18 19 19 19 10 10 10 10 10 10 10 10 10 10 10 10 10		function	onal moieties and one or more ionizable functional moieties, and wherein said compound
19		is capa	able of effecting the lysis of an endosome in response to a change in pH.
20			
21		6.	The endosomal lysing agent of claim 5, comprising a biocompatible compound.
22			
23	18).	The endosomal lysing agent of claim 5, comprising a biodegradable compound.
641	W,	/	
25		8.	The endosomal lysing agent of claim 5, comprising a biocompatible and biodegradable
26		compo	ound.
27			
28		9.	The endosomal lysing agent of claim 1, 2, 3, 4, 5, 6, 7, or 8 comprised of a polymer.
29			

The endosomallysing agent of claim 9, wherein the hydrolysis of said one or more 10. 1 hydrolyzable functional moieties effects a hydrophobic/hydrophilic transition of said compound. 2 3 The endosomal lysing agent of claim 10, wherein said hydrolysis further effects the 11. release of a compound capable of disrupting lipid bilayers. The endosomal lysing agent of claim 5, wherein said one or more ionizable functional 12. 7 moieties comprises proton acceptor sites. 8 -9 13. The endosomal lysing agent of/claim 1 or 5, wherein said one or more hydrolyzable 10 functionalities is independently selected from the group consisting of ortho-ester, hydrazone, and 11 cis-acetonyl 12 **2**13 The endosomal lysing agent of claim 13, wherein each of said ortho-ester containing monomers is selected from the group consisting of N-[2-methyl-1,3-O-ethoxyethylidineprpanediol]methacrylamide, ortho-ester derivatives of tartaric acid, ortho-ester derivatives of treitol, and ortho-ester derivatives of dithiothreitol. The polymerid lysing agent of claim 9, wherein the polymeric lysing agent is combined 15. in a form selected from the group consisting of: **1** 21 mixed polymers; 22 linear co-polymers branched co-polymers; and 23 dendrimer branched co-polymers. 16. The lysing agent of claim 9, wherein said agent is further functionalized with a targeting 26 agent selected from the group consisting of low density lipoproteins, transferrin, 27 asiaglycoproteins, gp120 envelope protein of human immunodeficiency virus, antibodies and 28 carbohydrates. 29

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<u>8 u</u>	par	17.	A biocompatible composition comprising:
	1	17.	a packaging agent, characterized by an ability to bind to a therapeutic agent and mediate
	2		
	3	ımporı	t into endosomes; and
	4		a lysing agent comprising a compound having one or more hydrolyzable functional
	5		es and wherein said compound is capable of effecting the lysis of an endosome in response
	6	to a ch	range in pH.
	7		,
	8 13) ^{18.}	The biocompatible composition of claim 17, wherein said compound further comprises
•	SAJO	one or	more ionizable functional moieties.
	10		
	11	19.	The biocompatible composition of claim 17 or claim 18, wherein said composition
1	12	compr	ises a polymer.
	13		,
1,7	14	20.	The biocompatible composition of claim 17 or 18, wherein said packaging agent and said
]]15	lysing	agent are combined in a form selected from the group consisting of:
	16		mixed polymers;
ij.	17:63	34)	linear co-polymers;
# #	ال اح 18		branched co-polymers; and
= = =	18 19 20		dendrimer branched co-polymers.
	20		
	21	21.	The biocompatible composition of claim 17 or claim 18, wherein said therapeutic agent
ŧ. <u>⊒</u>	22		ises a nucleic acid.
	23	1	
	24	22.	The biocompatible composition of claim 17 or claim 18, wherein the packaging agent
	25		ates with the therapeutic agent through a covalent interaction.
	26	ussoon	ates with the therapeatic agent through a covarent interaction.
	27	23.	The biocompatible composition of claim 17 or claim 18, wherein the packaging agent
	28	associa	ates with the therapeutic agent through a non-covalent interaction.
	29		

The composition of claim 17 or claim 18, wherein the packaging agent condenses the 24. 1 nucleic acid. 2 3 25. The composition of claim 17 or claim 18, wherein the packaging agent condenses the 4 nucleic acid to a size less than 150 nm. 5 6 26. The composition of claim 17 or claim 18, wherein the packaging agent comprises a 7 material with high charge density. 8 9 The composition of claim 26, wherein said packaging agent comprises a tertiary amine or 27. 10 a quaternary amine. 11 12 28. The composition of claim 27, wherein said packaging agent is selected from the group consisting of 2-[dimethylamino]ethyl methacrylate, (3-aminopropyl)methacrylamide, 2aminoethyl methacrylamide, aspartic acid, glutamic acid and polymers thereof. 16 **14**17 The composition of claim 17 or claim 18, wherein the hydrolysis of said one or more 29. 18 hydrolyzable functional moieties effects a hydrophobic/hydrophilic transition of said compound. The composition of claim 17 or claim 18, wherein said hydrolysis further effects the 30. release of a compound capable of disrupting lipid bilayers. - 21 22 The composition of claim 18, wherein said one or more ionizable functional moieties 23 31. comprises proton acceptor sites. 24 A cell delivery composition comprising: a compound to be delivered to a cell; 27 a delivery agent bound to the compound; and 28

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1	an endosomolytic agent comprising a compound capable of effecting the lysis of an			
2	endosome in response to a change in pH.			
3	•			
4	33. The cell delivery composition of claim 32, wherein said endosomolytic agent comprises a			
5	compound having one or more hydrolyzable functionalities			
6				
7	34. The cell delivery composition of claim 32, wherein said endosomolytic agent comprises a			
8	compound having one or more hydrolyzable functionalities and one or more ionizable			
9	functionalities.			
10				
11	35. The cell delivery composition of claim 32, wherein the compound to be delivered to a			
12	cell is selected from the group consisting of anti-AIDS substances, anti-cancer substances,			
13 13	antibiotics, immunosuppressants, anti-viral substances, enzyme inhibitors, neurotoxins, opioids,			
13 14 15 15 16 16 16 16 16 16 16 16 16 16 16 16 16	hypnotics, antihistamines, lubricants, tranquilizers, anti-convulsants, muscle relaxants, anti-			
₩ 115	Parkinson substances, anti-spasmodics and muscle contractants, miotics, anti-cholinergics, anti-			
16	glaucoma compounds, anti-parasite compounds, anti-protozoal compounds, anti-hypertensives,			
1917	analgesics, anti-pyretics, anti-inflammatory agents, local anesthetics, ophthalmics,			
<u>-</u> 18	prostaglandins, anti-depressants, anti-psychotic substances, anti-emetics, imaging agents,			
18 19 19 19 19 10 10 10 10 10 10 10 10 10 10 10 10 10	specific targeting agents, neurotransmitters, proteins, cell response modifiers, vaccines, anti-			
20	sense agents, RNA and ribozymes.			
21				
22	36. A non-immunogenic artificial virus less than 150 nm in size, comprising.			
23	a nucleic acid packaging agent;			
24	an endosomal lysing component capable of effecting the lysis of an endosome in			
25	response to a change in pH; and			
26	a nucleic acid.			
27				
28	37. The artificial virus of claim 36, wherein said endosomal lysing component comprises a			
29	compound having one or more hydrolyzable functionalities.			

	1	38.	The artificial virus of claim 36, wherein said endosomal lysing component comprises a
	2	compo	und having one or more hydrolyzable functionalities and one or more ionizable
	3	function	onalities.
	1 ⁴ 6		
<u>u</u>	P C.	3 9.	A method of lysing an endosome, the method comprising the steps of:
	6		providing a composition for endosomal uptake into the cell; and
	7		contacting the composition with the cell in the presence of an endosomal lysing agent
	8	capable	e of effecting the lysis of an endosome in response to a change in pH.
	9		
	10	40.	The method of claim 39 wherein said endosomal lysing agent comprises a compound
	11	having	one or more hydrolyzable functionalities.
	12		,
	13, 18	41.	The method of claim 39, wherein said endosomal lysing agent comprises a compound
<	Y4D ' /	having	one or more hydrolyzable functionalities and one or more ionizable functionalities.
	15 27		· ·
ū	Bail	42.	A method for introducing a therapeutic agent into a cell or a subcellular component, the
"U 1	17	method	d comprising the steps of:
	18		providing a biocompatible delivery composition comprising:
H	18 19		a packaging agent;
11	20		an endosomal lysing component capable of effecting the lysis of an endosome in
	20 21	respon	se to a change in pH; and
	22		a procleic acid; and
	23		contacting the composition with cells.
	24	•	
	25	43.	The method of claim 42, wherein said endosomolytic agent comprises a compound
	26	having	one or more hydrolyzable functionalities.
	27		
	28	44.	The method of claim 42, wherein said endosomolytic agent comprises a compound
4	295 B41	having	one or more hydrolyzable functionalities and one or more ionizable functionalities.
	-		•

- 1 45. The method of claim 42, further comprising contacting the composition with cells in the
- 2 absence of a known endosomal lysing component selected from the group consisting of
- 3 chloroquine, polyethyleneimine, fusogenic peptides, inactivated adenoviruses and combinations
- 4 thereof.

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